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# Dependence on over the counter (OTC) codeine containing analgesics: treatment and recovery with buprenorphine naloxone

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| **Corresponding Author:** | Marie Claire Van Hout, Ph.D<br>Waterford Institute of Technology<br>Waterford, IRELAND | |
| **Corresponding Author Secondary Information:** | | |
| **Corresponding Author's Institution:** | Waterford Institute of Technology | |
| **Corresponding Author's Secondary Institution:** | | |
| **First Author:** | Marie Claire Van Hout, Ph.D | |
| **First Author Secondary Information:** | | |
| **Order of Authors:** | Marie Claire Van Hout, Ph.D | |
| | Ide Delargy | |
| | Gerry Ryan | |
| | Siobhan Flanagan | |
| | Hugh Gallagher | |
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# Dependence on over the counter (OTC) codeine containing analgesics: treatment and recovery with buprenorphine naloxone

## Abstract

Misuse and dependence on prescribed and over the counter (OTC) codeine-combination analgesics is an emerging public health concern. We present a clinical case series of four adult patients dependent on OTC codeine combination analgesics in Ireland. Cases (two males/two females, aged 44–57 years) were consuming between 12 and 72 codeine-containing tablets/day. In three cases, consumption was linked to pain, with on-going misuse reflecting dependence on codeine. Cases were initiated on buprenorphine-naloxone (Suboxone®), stabilised on doses of between 4 mg/1 mg and 14 mg/ 3.5 mg per day and remain on treatment without additional opioid use, as verified by drug screening reports. Although anecdotal, these cases show the potential of effective opioid agonist treatment (OAT) using buprenorphine-naloxone (Suboxone®) to successfully treat this distinct form of opioid dependence disorder. Optimal service provision should recognise unique patient profiles and needs for this form of opioid dependence and incorporate psycho-social supports.

## Key Words

Codeine, opioid analgesic dependence, opioid painkiller dependence, buprenorphine-naloxone, Suboxone®

## Introduction

Addiction to opioids is defined as a chronic relapsing disorder characterised by permanent metabolic disorder (Dole and Nywsander, 1965). Diverse treatment approaches centre on the support of patients dependent on opioids and include long term opioid agonist treatment (OAT), detoxification, relapse prevention, psychosocial interventions and therapeutic communities (Amato et al., 2005; 2011). The use of several therapeutic agents is paramount in the management, stabilisation and detoxification of such patients, and includes the oral administration of full or partial opioid agonists such as methadone, buprenorphine, LAAM, codeine or morphine (Amato et al., 2005; Gowing et al., 2011; Riksheim et al., 2014).

Cochrane reviews have demonstrated strong evidence for effectiveness of methadone substitution treatment (Mattick et al., 2009; 2014), amid calls to scale up global availability in recent years (Mattick et al., 2009; Mathers et al., 2010). Methadone substitution is however controversial given the potential for fatal overdose, and long term and sometimes indefinite duration of treatment (Amato et al., 2005; Strike et al., 2013). Treatment retention is related to the prescribing of appropriate, individually determined and higher doses of methadone (Amato et al., 2005; Bao et al., 2013). Unpleasant withdrawals reported by methadone patients when tapering has contributed to the use of alternative therapeutic agents to support the patient such as clonidine, lofexidine, dihydrocodeine (DHC) and, more recently buprenorphine (Wright et al., 2007; Gowing et al., 2006;2009).

In terms of comparing methadone and buprenorphine, Cochrane reviews have determined that buprenorphine is an effective medication in the maintenance treatment of heroin dependence, retention of patients at doses above 2mg, and suppression of illicit opioid use at doses above 16mg based on placebo-controlled trials (Mattick et al., 2014). Mattick et al., (2014) also found high quality of evidence that buprenorphine was superior to placebo in treatment retention at all doses. However, methadone is superior to buprenorphine at patient retention,

with buprenorphine at flexible or low fixed doses resulting in poorer patient retention. No differences in effectiveness (retention and suppression of illicit opioid use) between methadone and buprenorphine are observed when fixed medium or high doses are used (Mattick et al., 2014). Hser et al., (2014) also reported on the association of methadone with enhanced treatment retention when compared to buprenorphine, but with provision of buprenorphine related to lower continued use of illicit opioids. In terms of patient completion of treatment, Gowing et al., (2006; 2009) in their Cochrane Reviews found no significant differences between methadone and buprenorphine, but reported that buprenorphine achieves faster reduction of withdrawal symptoms, and is more effective than clonidine in the management of opioid withdrawals. Sublingual buprenorphine-naloxone may also cause less fatal intoxications than methadone (Soyka, 2015).

Cost of treating with methadone is less than with buprenorphine (Connock et al., 2007). Maas et al., (2013) in their economic evaluation of buprenorphine versus methadone in opiate substitution treatment, emphasise that buprenorphine is appropriate if cessation of opiate use plus retention are primary outcomes. Gouveia et al., (2015) in their cost –effectiveness and cost utility of fixed dose combination of buprenorphine-naloxone versus methadone in substitution treatment, concluded that the buprenorphine-naloxone combination is cost-effective (acquisition, preparation and transport of medication, cost of dispensing, supervision of administration, patient monitoring and non-medical direct costs of crime related to drug addiction) and can potentially generate health gains measured using number of heroin free days per year and quality adjusted life years (QALYs) in the target patient population at a low cost. Mutlu and Bilici (2015) have also recently reported on the effectiveness of outpatient buprenorphine-naloxone maintenance therapy in Turkey, which can be enhanced with incorporation of psychosocial supports.

Codeine dependence has emerged as recent public health concern and is underpinned by widespread availability for the symptomatic relief of mild to moderate pain or cough (UNODC, 2011; Van Hout and Norman, 2015), with an increasing evidence base highlighting diverse forms of misuse of and dependence on codeine containing analgesics in Australia, South Africa, the United Kingdom, France and the United States (Van Hout et al., 2014). The issue of iatrogenic opioid analgesic dependence confounds treatment pathways and recovery outcomes (Stannard, 2013; Marr and Hill 2015). Adverse health harms are also reported on excessive or high dose consumption of combination analgesics containing codeine with paracetamol or ibuprofen (Lambert and Close, 2005; Dutch, 2008; Evans et al., 2010; Ernest et al., 2010; Frei et al., 2010; Ng et al., 2011) and with increases in mortality reported (Pilgrim et al., 2013; Handley and Flanagan, 2014). Increases in patient attendance of health services for opioid analgesic dependency are also reported, particularly in countries where available in over the counter (OTC) codeine containing formulations (Myers et al., 2003; McDonough, 2011; Stannard, 2013; Nielsen et al., 2015a).

Whilst qualitative studies in the UK, South Africa, Australia and Ireland have investigated the experiences of individuals dependent on codeine (Nielsen et al., 2010; 2011; Nielsen et al., 2013; Cooper, 2011, 2013; Van Hout, 2015; Van Hout et al., 2015a; b), scant attention has been paid to the design and provision of appropriate and specific treatment modalities for codeine dependence (Marr and Hill, 2015; Nielsen et al., 2015b). Studies show that individuals experiencing codeine dependence are different to other opioid dependent groups (Nielsen et al., 2011; Nielsen et al., 2015c). Patient's often lack of recognition of their problematic codeine use, with a perception of themselves as 'different' to drug addicts, with stigma relating to addiction treatment (particularly methadone) and with the blurring between therapeutic and problematic use confounding treatment uptake (Nielsen et al., 2010; Reed et al., 2011; Kean, 2015).

Until recently, there is a limited evidence base to underpin best practice guidelines for OAT in this type of opioid dependent patient (Cooper, 2013; Conroy and Hill, 2014; Hard, 2014) with guidelines generally concerning treatment of illicit drug use (National Institute for Health and Clinical Excellence, 2007). Buprenorphine-naloxone whilst generally used for treatment of heroin dependence, is an effective opioid agonist treatment for prescription and OTC opioid analgesic dependence(Sigmon et al., 2009; Weiss et al., 2011), and is reported to benefit patients presenting with codeine dependence (Department of Health -England and the Developed Administrations, 2007; Stannard, 2013; Royal College of General Practitioners, 2014). It has more recently been investigated for use in codeine dependence in Australia (Nielsen et al., 2015b). Recent case studies in the UK have also indicated successful treatment experiences and recovery outcomes using buprenorphine-naloxone (Hard, 2014; Conroy and Hill, 2014; Kean, 2015; Marr and Hill, 2015). Decisions to use buprenorphine-naloxone are underpinned by its safety profile compared to methadone (ceiling effect on respiratory depression and lower abuse potential), lack of association with QT prolongation, fewer symptoms of withdrawal when discontinued, and enhanced ability to continue occupational and social functioning (in contrast to methadone) due to greater clarity of thought (Conroy and Hill, 2014; New Zealand Ministry of Health, 2014; Fiellin et al., 2014; Hard, 2014).

Most current data in Ireland indicates that 1.9% of patients in drug treatment reported codeine as a primary or secondary drug of abuse in the time period 2008-2012 (personal communication from the National Drug Treatment Reporting System). For patients requiring OAT, the most widely prescribed treatment in Ireland is methadone. At the time of writing, buprenorphine-naloxone (Suboxone®) is now prescribed to 77 patients in selected dispensing clinics in Ireland. We report four Irish cases of dependence on OTC codeine-combination analgesics (containing codeine-ibuprofen) and describe treatment and on-going recovery with buprenorphine-naloxone through a pilot feasibility project. Initiation of treatment using buprenorphine-naloxone was chosen for these specific cases for the following reasons; whilst

they often present with similar underlying issues of trauma, they are generally better functioning in terms of social and occupation, and are often in employment. They generally dislike the sedating effect from OAT and are subsequently commenced on Suboxone® where available. The faster induction facilitates easier transferal to OAT, the cessation of use of OTC codeine containing medicines relatively easily in one day, and with easier stabilisation. Safe titration to a sufficient dose of methadone would have taken several weeks, during which time concomitant opioids are required to prevent withdrawal and with the final high dose of methadone potentially posing an overdose risk.

## Case One

A 57-year old married healthcare professional presented to her general practitioner (GP) because of a single episode of haematemesis that morning. The case admitted to misuse of OTC codeine-ibuprofen. Her GP was aware that the case had suffered a broken wrist 3 years earlier and had taken codeine-ibuprofen at the time for pain. After ordering blood tests and satisfied that the bleed was most likely related to her high consumption of codeine-ibuprofen, she was referred to the local dependency/addiction service where a detailed history revealed the full extent of the case's analgesic consumption, and the degree to which it had damaged her life. The case had been aware of her growing dependence over time, but her use escalated from 12 tablets per day to 24–48 tablets a day over a three-year period since the fracture. Aware of her problem, she reported that she '***could not survive 1 day without taking the tablets'*** and would visit different chemists far from her home and pay people to buy the tablets for her. The on-going use gave her a ***'high'*** as well as experiencing dissociation from herself. The case neglected her appearance and her family's needs, became estranged from her children and was no longer able to work.

The case was counselled and agreed to begin opioid agonist treatment (OAT). At the time, treatment with buprenorphine-naloxone was available through a pilot feasibility project in

Ireland. To begin, the case did not consume codeine for 24 hours. Treatment initiation was uneventful—the case experienced discomfort for most of the day and was stabilised on a 4 mg/1 mg dose of buprenorphine-naloxone. As part of her on-going recovery, she speaks to a counsellor every two weeks, and her doctor once a month. After four years of OAT, all drug screens have been negative. She continues to receive supervised buprenorphine-naloxone from the local pharmacy. She has gradually reduced her dose over the last 2 years and is currently stable with the expectation of treatment discontinuation in the near future. Her self-confidence has returned over time, and the case has become reconciled with her family.

## Case Two

A 44-year old divorced, working mother was contacted by her GP after he received questions from a pharmacist about the case's high-volume use of codeine-ibuprofen and from the same case's employer about the case's sick notes. The case came into the practice and after hearing her GP's concerns, admitted altering the GP's letters to cover up her high volume use of OTC analgesics. Her GP immediately recognised her dependence on codeine and referred her to addiction services. On presentation to the addiction clinic, the case described a 10-year history of debilitating migraines and depression. Initially prescribed co-codamol for a short period, she regularly used OTC co-codamol and codeine-ibuprofen on top of her prescription. After a traumatic personal event (the end of her marriage), the case was diagnosed with depression and prescribed antidepressants. During this time she began to escalate her use of OTC drugs. On a normal day she would consume 36 tablets, travelling to different pharmacies every day to avoid suspicion and took her mother or friend's prescriptions for opioid-containing medications whenever possible. The addiction clinic discussed with her and recommended buprenorphine-naloxone, which was available through the pilot project in Ireland.

At commencement of OAT, the case was attending the local community mental health team and was under the care of a psychiatrist and prescribed venlafaxine for depression, propranolol for migraine and omeprazole for a peptic ulcer. She was initiated onto buprenorphine-naloxone after 24 hours without codeine consumption and although concerned about withdrawal, it was less severe than she anticipated with symptoms limited to itching, sweating, and headache. After stabilising on a 14 mg/3.5 mg dose, her migraines largely resolved and soon after treatment, she was able to stop antidepressant treatment. The case is currently attending the addiction clinic twice a week with on-going psychosocial counselling. She reports ***'finally I feel normal again and have the energy to get through the day and get on with things'*** and has returned to work. Within the next few months, the pathway from maintenance to detoxification will be addressed with this case.

### Case Three

A 45-year old single man with a past history of alcohol dependence and on-going benzodiazepine use with comorbid severe personality difficulties had a long history of OTC codeine misuse that was causing life-threatening morbidity. He had suffered a perforated ulcer in 2012, which required surgical repair. In addition he developed pancreatitis and partial Addison's disease due to dihydrocodeine misuse. In early 2014, he was found to have three chronic ulcers—one gastric ulcer and two in the duodenal. He had multiple surgical admissions due to the severity of his epigastric pain and GI bleeding. Typically his symptoms would quickly improve, but he continued to misuse OTC analgesics on discharge. In view of this a partial or total gastrectomy was being considered.

Prior treatments had failed. He had undergone several community and inpatient detoxifications from codeine but quickly relapsed on each occasion. Several attempts to stabilise him on a maintenance dose of codeine in the community had also failed. In 2010, a trial of buprenorphine was initially successful for three months but due to benzodiazepeine

use on top, he overdosed on benzodiazepines, was hospitalised and buprenorphine treatment was withdrawn. Due to the extent of his ulceration, the severity of his pain and the chronic nature of his addiction, the best treatment course were not obvious. He did not want gastric surgery and understood that on-going misuse of OTC analgesics would shorten his life. He wished a further trial on OAT. He understood that buprenorphine/naloxone would be dispensed from the community pharmacy with supervised daily consumption, and that the treatment would also involve regular attendance with a keyworkers for psychosocial support. He was admitted to the addictions unit in May 2014 to manage OAT initiation, which was successful. He was stabilised, and is currently maintained on a dose of 12 mg/3 mg buprenorphine-naloxone. His urine drug screens have remained consistently opiate and benzodiazepine free although cannabis positive. He has never presented sedated or intoxicated, attends regularly for his script and has had a great reduction in gastric pain He has had two very brief admissions with gastritis which settled quickly with conservative management.

### Case Four

A 44-year old divorced, homeless man presented to his community drug service in a poor physical health. Originally prescribed codeine for back pain, over the course of several years he began using escalating amounts of OTC codeine-ibuprofen analgesics, with peak consumption reaching 72 tablets/day. He found that codeine sedated the depression he was experiencing with losing his job, but he began to consume too much alcohol and eventually his family situation broke down and he became homeless. During his time in homeless services he had also begun using other substances including hypnotics. The case had a pre-existing heart condition which was exacerbated by his codeine-ibuprofen consumption.

He was assessed and referred to the National Drug Treatment Centre, where he underwent psychiatric assessment, urine screening and was initiated onto buprenorphine-naloxone in

conjunction with psychosocial interventions. He was initiated and stabilised on a maintenance dose of 8 mg/2 mg daily with on-going counselling. Soon after, he was referred for rehabilitation. After 11 months of buprenorphine-naloxone treatment, the case was taking unsupervised doses and attempted to detoxify from treatment without medical supervision. At day 6, he relapsed. He revealed to his key worker that he had not fully disclosed his excessive alcohol intake or his intermittent misuse of cough bottles. The case was counselled and again initiated onto buprenorphine-naloxone. He is currently stabilised on a dose of 12mg daily with on-going psychosocial support. Currently he is still experiencing misuse issues with cannabis and benzodiazepines.

## Discussion

The heterogeneous nature of codeine misuse and varying profile of treatment case's for codeine dependence is evident, given their distinct characteristics from other opiate using populations, and they often require alternative forms of treatment provision and therapeutic modalities (Nielsen et al., 2011; Hard, 2014; Nielsen et al, 2015a). These four cases from Ireland highlight the wide spectrum of people who become dependent on OTC codeine-combination analgesics, from a male case with a long history of complex and multiple addictions and personality difficulties and with a strong family history of addiction, to middle-aged husbands and wives whose initial consumption of codeine was linked to a legitimate pathology. In all four cases, the dependence was associated with codeine-ibuprofen combination analgesics, attending multiple pharmacies to obtain tablets, persistent psychological problems that disrupted normal life and finally significant morbidity linked to the misuse. Similar findings are reported elsewhere (Nielsen et al., 2010; 2011; Nielsen, Cameron & Pahoki, 2013; Cooper, 2011, 2013; Van Hout, 2015; Van Hout et al., 2015a;b). The cases of GI haemorrhage and ulcer perforation also align closely with previous descriptions of codeine-ibuprofen dependency (Lambert and Close, 2005; Dutch, 2008; Evans et al., 2010; Ernest et al., 2010; Frei et al., 2010; Ng et al., 2011).

Codeine has lower potency than other opioids (for example heroin, methadone, morphine, oxycodone), with codeine dependent individuals using lower doses of opioids when compared to oral morphine equivalents (Nielsen et al., 2015c). Nielsen et al., (2015b) highlight that whilst lower potency of codeine is consumed, buprenorphine dose requirements for codeine dependence cannot be assumed to generalise that of heroin dependence, despite evidence for consistently higher doses of buprenorphine estimations based on dose of codeine consumed, and comparability to that of heroin and more potent prescription opioid treatment. This Australian study revealed concerns that clinicians using standard opioid dose conversion calculations (Fine and Portenoy, 2009) are at risk of underestimating required dose of buprenorphine, and can potentially reduce clinical outcomes (Doran et al., 2005; Mattick et al., 2014). Individual dose titration is best practice (Gowing et al., 2014), with high dose buprenorphine appearing to be well tolerated and safe (Nielsen et al., 2015b). The recommendation is that codeine dependent patients receive doses similar to that of other opioid dependent people (Nielsen et al., 2012) in the 16-32 mg/day range (Fareed et al., 2012). Higher doses may also improve retention (Fareed et al., 2012).

Although anecdotal, these cases are typical of other cases of codeine dependence we have treated. For the patients described here, OAT using buprenorphine-naloxone has been successful, with patients returning to a better psychological state and functioning again within their families and/or within society. They highlight the problem of OTC codeine combination analgesic dependence and show the potential of effective OAT using buprenorphine-naloxone coupled with psychosocial counselling to successfully treat this form of opioid dependence. This is supported by case studies conducted in the UK (Conroy and Hill, 2014; Hard, 2014; Kean, 2015) which have highlighted the need for buprenorphine-naloxone programming within a holistic behaviour change programme with incorporated psycho-social intervention and recovery supports.

## Conclusion

We underscore how opioid based prescription/OTC medication dependence warrants alternative low threshold service provision in primary care, and one that is tailored to the differences between iatrogenic opioid dependence and that of illicit opioids (Marr and Hill, 2015). Additional differences pointing to the need for buprenorphine-naloxone as treatment options are underpinned by demographic and substance use characteristics of codeine dependents (Nielsen et al., 2011; Nielsen et al., 2015c). Distinguishing iatrogenic dependence as opposed to that of illicit drug use also reduces stigma and facilitates enhanced treatment entry for pain patients (Marr and Hill, 2015). The cases highlighted the need for prescriber and pharmacist assessment of risk of developing codeine dependence through routine screening (Hard, 2014). Primary care physicians are advised to consider potential iatrogenic opioid dependence in patients (Hard, 2014). In 2010, the Irish pharmacy regulator (Pharmaceutical Society of Ireland) enforced new regulations to regulate the safe supply of non-prescription combination products containing codeine and paracetamol, aspirin or ibuprofen for supply only as ‘second line’ products for pain relief; and with comprehensive patient advice provided around correct use for short-term use (for example no longer than three days), and with products inaccessible to the public for self-selection.

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## Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

## Conflict of interest

Authors declare they have no conflict of interest.

## References

Amato L, Davolia M, Peruccia CA, Ferria M, Faggiano F, & Mattick RP. (2005). An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *Journal of Substance Abuse Treatment*, 28(4):321–9. doi:10.1016/j.jsat.2005.02.007.

Amato L, Minozzi S, Davoli M, & Vecchi S. (2011). Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database of Systematic Reviews*, 10: CD004147. doi:10.1002/14651858.CD004147.pub4.

Auriacombe M, Fatséas M, Dubernet J, Daulouède JP, & Tignol J. (2004). French field experience with buprenorphine. *The American Journal on Addictions*, 13 Suppl1:S17–S28. Doi: 10.1080/10550490490440780

Bao Y, Liu Z, Epstein DH, Du C, Shi J, & Lu L. (2009). A meta-analysis of retention in methadone maintenance by dose and dosing strategy. *The American Journal of Drug and Alcohol Abuse*, 35(1):28-33. doi: 10.1080/00952990802342899.

Connock M, Juarez Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, Fry-Smith A, Day E, Lintzeris N, Roberts T, Burls A, & Taylor RS. (2007). Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technology Assessment*, 11(9):1-171, iii-iv. doi:http://dx.doi.org/10.3310/hta11090

Conroy S, & Hill D. (2014). Failure to identify or effectively manage prescription opioid dependence acted as a gateway to heroin use—buprenorphine/naloxone treatment and recovery in a surgical patient *BMJ Case Reports*, pii: bcr2014207458. doi:10.1136/bcr-2014-207458

Cooper RJ. (2013): 'I can't be an addict. I am.' Over-the-counter medicine abuse: a qualitative study. *BMJ Open*, 3(6). pii: e002913. doi: 10.1136/bmjopen-2013-002913.

Conroy S, & Hill D. (2014): Failure to identify or effectively manage prescription opioid dependence acted as a gateway to heroin use—buprenorphine/naloxone treatment and

recovery in a surgical patient. *BMJ Case Reports*, pii: bcr2014207458. doi: 10.1136/bcr-2014-207458.

Cooper R. (2011). *Respectable addiction - a qualitative study of over the counter medicine abuse in the UK.* University of Sheffield: School of Health and Related Research (ScHARR).

Department of Health (England) and the devolved administrations. (2007). *Drug misuse and dependence: UK Guidelines on Clinical Management.* London. Department of Health (England), the Scottish Government, Welsh Assembly and Northern Ireland Executive.

Dole VP, & Nywsander M. (1965). A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. *The Journal of the American Medical Association*, 193(8):646-50. doi:10.1001/jama.1965.03090080008002.

Doran CM, Holmes J, Ladewig D, & Ling W. (2005). Buprenorphine induction and stabilisation in the treatment of opiate dependence. *Heroin Addiction and Related Clinical Problems,* 7(1):7–18.. doi: 10.1016/j.jsat.2011.12.009

Dutch MJ. (2008). Nurofen Plus misuse: an emerging cause of perforated gastric ulcer. *The Medical Journal of Australia*,188(1):56–7.

Ernest D, Chia M, & Corallo CE. (2010). Profound hypokalaemia due to Nurofen Plus and Red Bull misuse. *Critical care and resuscitation*, 12(2):109–10.

Evans C, Chalmers-Watson TA, & Gearry RB. (2010). Medical Image. Combination NSAID-codeine preparations and gastrointestinal toxicity. *New Zealand Medical Journal*,123(1324):92–3.

Fareed, A, Vayalapalli S, Casarella J, & Drexler K. (2012). Effect of Burprenorphine Dose on Treatment Outcome. *Journal of Addictive Diseases*, 31(1):8–18. doi: 10.1080/10550887.2011.642758.

Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, & O'Connor PG. (2014): Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. *JAMA Internal Medicine*, 174(12): 1947-54. doi: 10.1001/jamainternmed.2014.5302.

Fine PG, & Portenoy RK, Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation. (2009) . Establishing 'Best Practices' for opioid rotation: conclusions of an expert panel. *Journal of Pain and Symptom Management*,38(3):418–25. doi: 10.1016/j.jpainsymman.2009.06.002.

Frei MY, Nielsen S, Dobbin M, & Tobin CL. (2010). Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases. *The Medical Journal of Australia*, 193(5): 294-6.

Gouveia M, Sousa R, Costa J, & Borges M. (2015). Economic evaluation of Suboxone® for substitution treatment of opioid drug dependence in Portugal. *Heroin Addiction and Related Clinical Problems*, 17(1): 43-50.

Gowing L, Ali R, Dunlop A, Farrell M, & Lintzeris N. (2014). *National Guidelines for Medication-Assisted Treatment of Opioid Dependence.* Canberra: National Drug Strategy.

Gowing L, Ali R, & White JM. (2009). *Buprenorphine for the management of opioid withdrawal.* Cochrane Database of Systematic Reviews, 3:CD002025.DOI:10.1002/14651858.CD002025.pub4.

Gowing, L, Farrell MF, Bornemann R., Sullivan LE, & Ali R. (2011). *Oral substitution treatment of injecting opioid users for prevention of HIV infection.* Cochrane Database of Systematic Reviews, 8:CD004145. doi: 10.1002/14651858.CD004145.pub4.

Handley SA, & Flanagan RJ. (2014). Drugs and other chemicals involved in fatal poisoning in England and Wales during 2000–2011. *Clinical Toxicology* ,52(1):1–12. doi: 10.3109/15563650.2013.872791.

Hard B. (2014). Management of opioid painkiller dependence in primary care: ongoing recovery with buprenorphine/naloxone. *BMJ Case Reports*, pii: bcr2014207308. doi:10.1136/bcr-2014-207308

Hser Y, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya,C, McLaughlin P, Wiest K, Cohen A, & Ling W, (2014). Treatment retention among patients

randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction*,109(1): 79–87. doi:10.1111/add.12333.

Lambert AP, & Close C. (2005). Life-threatening hypokalaemia from abuse of nurofen plus. *Journal of the Royal Society of Medicine*,98(1):21. doi: 10.1258/jrsm.98.1.21.

Maas J, Barton G, Maskrey V, Pinto H, & Holland R. (2013). Economic evaluation: a comparison of methadone versus buprenorphine for opiate substitution treatment. *Drug and Alcohol Dependence*, 133(2):494-501. doi: 10.1016/j.drugalcdep.2013.07.018.

Marr E, & Hill D (2015). Optimising service provision for prescribed opioid analgesic dependence. *Heroin Addiction and Related Clinical Problems*,17(5): 13-8.

Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick RP, Myers B, Ambekar A, & Strathdee SA; (2010). HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. *Lancet*, 375(9719):1014–28. doi: 10.1016/S0140-6736(10)60232-2.

Mattick RP, Breen C, Kimber J, & Davoli M. (2014). *Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence.* Cochrane Database of Systematic Reviews, 2:CD002207. doi:10.1002/14651858.CD002207.pub4.

Mattick RP, Breen C, Kimber J, & Davoli M. (2009). *Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence.* Cochrane Database of Systematic Reviews, 3:CD002209. doi:10.1002/14651858.CD002209.pub2.

McDonough MA. (2011). Misuse of codeine-containing combination analgesics. *The Medical Journal of Australia*, 194(9):486.

Ministry of Health. (2014). *New Zealand Practice Guidelines for Opioid SubstitutionTreatment.* Wellington: Ministry of Health.

Mutlu E, Bilici R. (2015). Outcomes of buprenorphine-naloxone maintenance therapy: One-year follow up study from Turkey. *Heroin Addiction and Related Clinical Problems*, 17(1): 79-90.

Myers B, Siegfried N, & Parry CD. (2003). Over-the-counter and prescription medicine misuse in Cape Town -findings from specialist treatment centres. *South African Medical Journal*, 93(5), 367-70.

National Institute for Health and Clinical Excellence (NICE) (2007). *Drug misuse in over 16s. Opioid detoxification.* Clinical guideline 52. London: NICE.

Ng JL, Morgan DJ, Loh NK, Gan SK, ColemanPL, Ong GS, & Prentice D. (2011). Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. *The Medical Journal of Australia*,194(6):313–6..

Nielsen S, Roxburgh A, Bruno R, Lintzeris N, Jefferson A, Degenhardt L. (2015a). Changes in non-opioid substitution treatment episodes for pharmaceutical opioids and heroin from 2002 to 2011. *Drug and Alcohol Dependence*, 149: 212-9. doi:10.1016/j.drugalcdep.2015.02.004.

Nielsen S, Bruno R, Murnion B, Dunlop A, Degenhardt L, Demirkol A, Muhleisen P, Lintzeris N. (2015b). Treating codeine dependence with buprenorphine: Dose requirements and induction outcomes from a retrospective case series in New South Wales, Australia. *Drug and Alcohol Review*. Early Online. doi: 10.1111/dar.12315.

Nielsen S, Murnion B, Dunlop A, Degenhardt L, Demirkol A, Muhleisen P, Litzeris N. (2015c). Comparing treatment-seeking codeine users and strong opioid users: findings from a novel case series. *Drug and Alcohol Review*,34(3):304–11. doi: 10.1111/dar.12315.

Nielsen S, Cameron J, & Pahoki S. (2013). Opportunities and challenges: Over-the-counter codeine supply from the codeine consumer's perspective. *The International Journal of Pharmacy Practice,* 21(3), 161-8. doi: 10,1111/j.2042-7174.2012.00247.x.

Nielsen S, Hillhouse M, Mooney L, Fahey J, Ling W. (2012). Comparing buprenorphine induction experience with heroin and prescription opioid users. *Journal of Substance Abuse Treatment*, 43(3):285–90. doi: 10.1016/j.jsat.2011.12.009.

Nielsen S, Cameron J, & Lee N. (2011). Characteristics of a nontreatment-seeking sample of over-the-counter codeine users: implications for intervention and prevention. *Journal of Opioid Management*, 7(5): 363-370.

Nielsen, S., Cameron, & Pahoki, S. (2010). *Over-the-counter codeine dependence.* Melbourne, Australia: The Turning Point Alcohol and Drugs Centre.

Pilgrim JL, Dobbin M, Drummer OH. (2013). Fatal misuse of codeine-ibuprofen analgesics in Victoria, Australia. *The Medical Journal of Australia,* 199(5):329–31. doi:10.5694/mja12.11843

Reed K, Bond A, Witton J, Cornish R, Hickman M, & Strang J. (2011). *The changing use of prescribed benzodiazepines and z-drugs and of over-the-counter codeine-containing products in England: a structured review of published English and international evidence and available data to inform consideration of the extent of dependence and harm.* London. National Addiction Centre.

Riksheim M, Gossop M, & Clausen T. (2013). From methadone to buprenorphine: changes during a 10 year period within a national opioid maintenance treatment programme. *Journal of Substance Abuse Treatment,* 46(3):291–4. doi: 10.1016/j.jsat.2013.10.006.

Sigmon SC, Dunn KE, Badger GJ, Heil SH, & Higgins ST. (2009). Brief buprenorphine detoxification for the treatment of prescription opioid dependence: a pilot study. *Addictive Behaviours*,34(3):304–11. doi: 10.1016/j.addbeh.2008.11.017.

Soyka M. (2015). New developments in the management of opioid dependence: focus on sublingual buprenorphine-naloxone. *Substance Abuse and Rehabilitation,* 6:1-14. doi: 10.2147/SAR.S45585.

Stannard C (2013). Opioids in the UK: what's the problem? *BMJ,* 347:f5108. doi: 10.1136/bmj.f5108

Van Hout MC. (2015) Nod and Wave: an Internet study of the codeine intoxication phenomenon. *International Journal of Drug Policy,* 26 (1),67-77. doi:10.1016/j.drugpo.2014.06.016.

Van Hout MC, Bergin M, Foley M, Rich E, Rapca AI, Harris R, & Norman I. (2014). *A Scoping Review of Codeine Use, Misuse and Dependence, final report.* CODEMISUSED Project European Commission 7th Framework Programme, EU. Brussels.

Van Hout MC, Horan A,Santlal K, Rich E, Bergin M. (2015a). 'Codeine is my Companion': Misuse and dependence on codeine containing medicines in Ireland. *Irish Journal of Psychological Medicine.* Early Online.

Van Hout MC, Rich E, Dada S, Bergin M. (2015b). Codeine is my Helper: A qualitative study of pharmacy access and codeine misuse in South Africa. *Qualitative Health Research.* Early Online. doi: 10.1177/1049732315613764

Van Hout MC, & Norman I. (2015). Misuse of non-prescription codeine containing products: Recommendations for detection and reduction of risk in community pharmacies. *International Journal of Drug Policy*, Early Online. doi: 10.1016/j.drugpo.2015.09.007.

Weiss RD, Potter JS, Fiellin D, Byrne M, Connery HS, Dickinson W, Gardin J, Griffin ML, Gourevitch MNm Haller DL, Hasson AL, Huang Z, Jacobs P, Kosinski AS, Lindblad R, McCance-Katz EF, Provost SE, Selzer J, Somoza EC, Sonne SC, & Ling W. (2011). Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for presciption opioid dependence: a 2-phase randomized controlled trial. *Archives of General Psychiatry*, 68(12):1238–46. doi: 10.1001/archgenpsychiatry.2011.121

Wright NMJ, Sheard L, Tompkins CNE, Adams CE, Allgar VL, & Oldham NS. (2007). Buprenorphine versus dihydrocodeine for opiate detoxification in primary care: a randomised controlled trial. *BMC Family Practice*, 8:3. doi:10.1186/1471-2296-8-3.g

# Dependence on over the counter (OTC) codeine containing analgesics: treatment and recovery with buprenorphine naloxone

Marie Claire Van Hout [1], Ide Delargy[2], Gerry Ryan[3], Siobhan Flanagan[4], Hugh Gallagher[5]

[1] Principal Investigator CODEMISUSED, School of Health Sciences, Waterford Institute of Technology, Ireland. mcvanhout@wit.ie

[2] GP, Blackrock Family Practice, Blackrock, Co Dublin; Director, Substance Misuse Programme, Irish College of General Practitioners. ide.delargy@icgp.ie

[3] Project Manager, Tolka River Project, Dublin. tolkariverproject@gmail.com

[4] South Eastern Trust, Downshire Hospital, Downpatrick, Co Down, UK
siobhan.flanagan@setrust.hscni.net

[5] GP Coordinator, Addiction Services Dublin North City, and County Dublin, Ireland.
hugh.gallagher@hse.ie

**Corresponding author:**

Dr Marie Claire Van Hout, Principal Investigator CODEMISUSED, School of Health Sciences, Waterford Institute of Technology, Ireland.

+35351845548

mcvanhout@wit.ie